

# Role of Wingless (Wg) signaling pathway in A $\beta$ 42 mediated neurodegeneration in Alzheimer's disease

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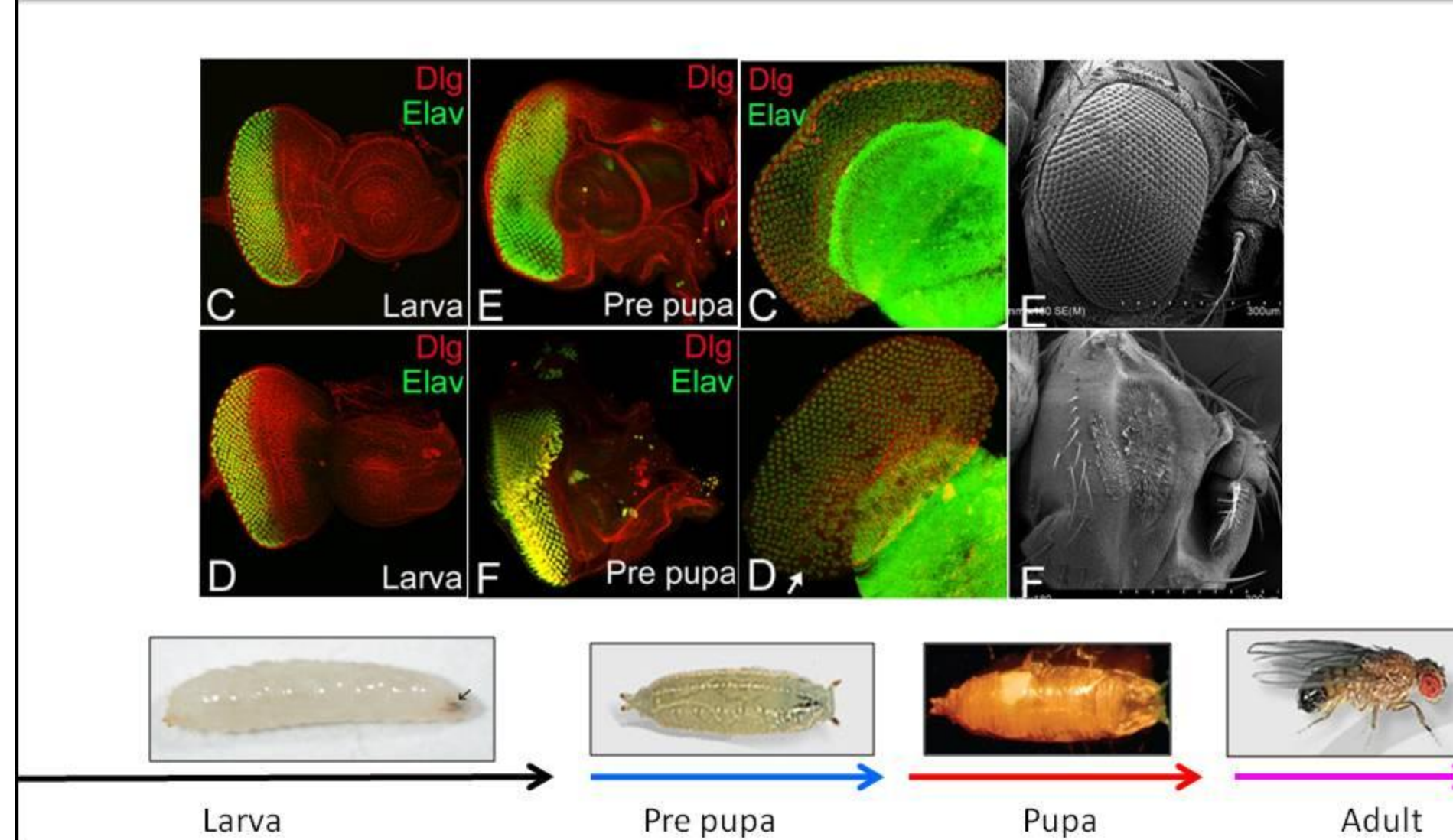
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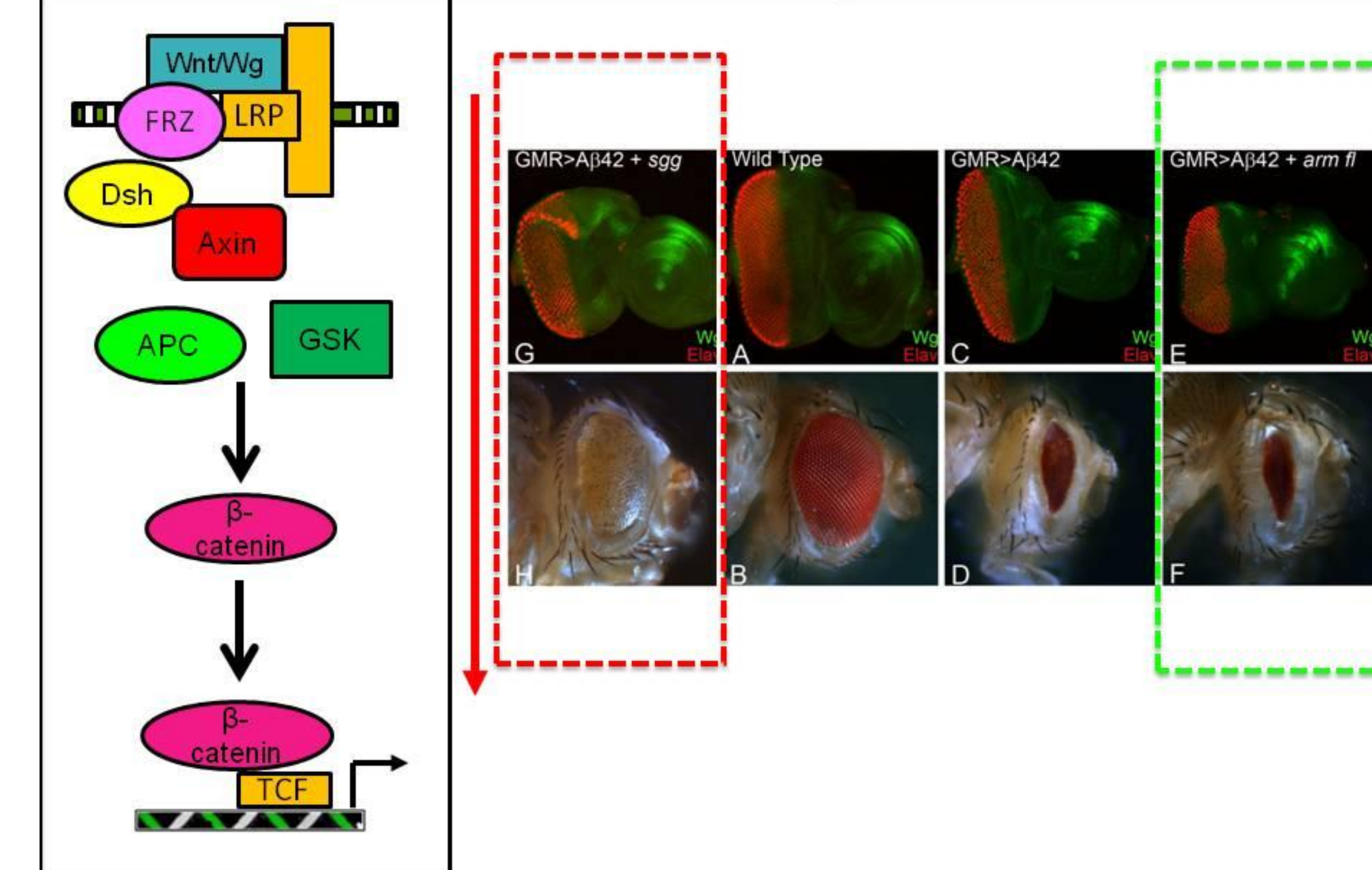
## Abstract

Alzheimer's disease (AD), an age related progressive neurodegenerative disorder manifests as memory loss and reduced cognitive ability. One of the hallmarks of AD is formation of the Amyloid-beta (hereafter A $\beta$ 42) plaques, which initiates oxidative stress due to impaired signaling and finally leads to the death of neurons by unknown mechanism. However the exact mechanism causing cell death is still not well understood. We misexpressed high levels of human A $\beta$ 42 protein in the developing fly retina, which mimics AD like neuropathology. In a forward genetic screen we have identified members of highly conserved Wingless (Wg) signaling pathway as modifiers of the A $\beta$ 42 mediated neurodegeneration. Furthermore, Wg protein levels are upregulated in the dying cells marked by TUNEL staining. We have demonstrated that blocking Wg signaling pathway, by misexpressing negative regulator of Wg like Shaggy kinase (sgg) or a dominant negative form of Drosophila T-cell factor (dTCF<sup>DN5</sup>) or blocking Wg transport specifically by downregulating Porcupine (using porcupineRNAi) can rescue A $\beta$ 42 mediated neurodegeneration by reducing the number of dying cells and restoring the axonal targeting from the retina to the brain. We have developed a drug feeding regimen for flies and will test if we can use chemical inhibitors to block Wg signaling in neurons expressing high levels of A $\beta$ 42 and thereby prevent neurodegeneration in the Drosophila eye. We will test antagonists and agonist of Wg signaling to determine if they can work as chemical inhibitor/modifier of A $\beta$ 42 mediated neurodegeneration. The results from our studies will be presented.

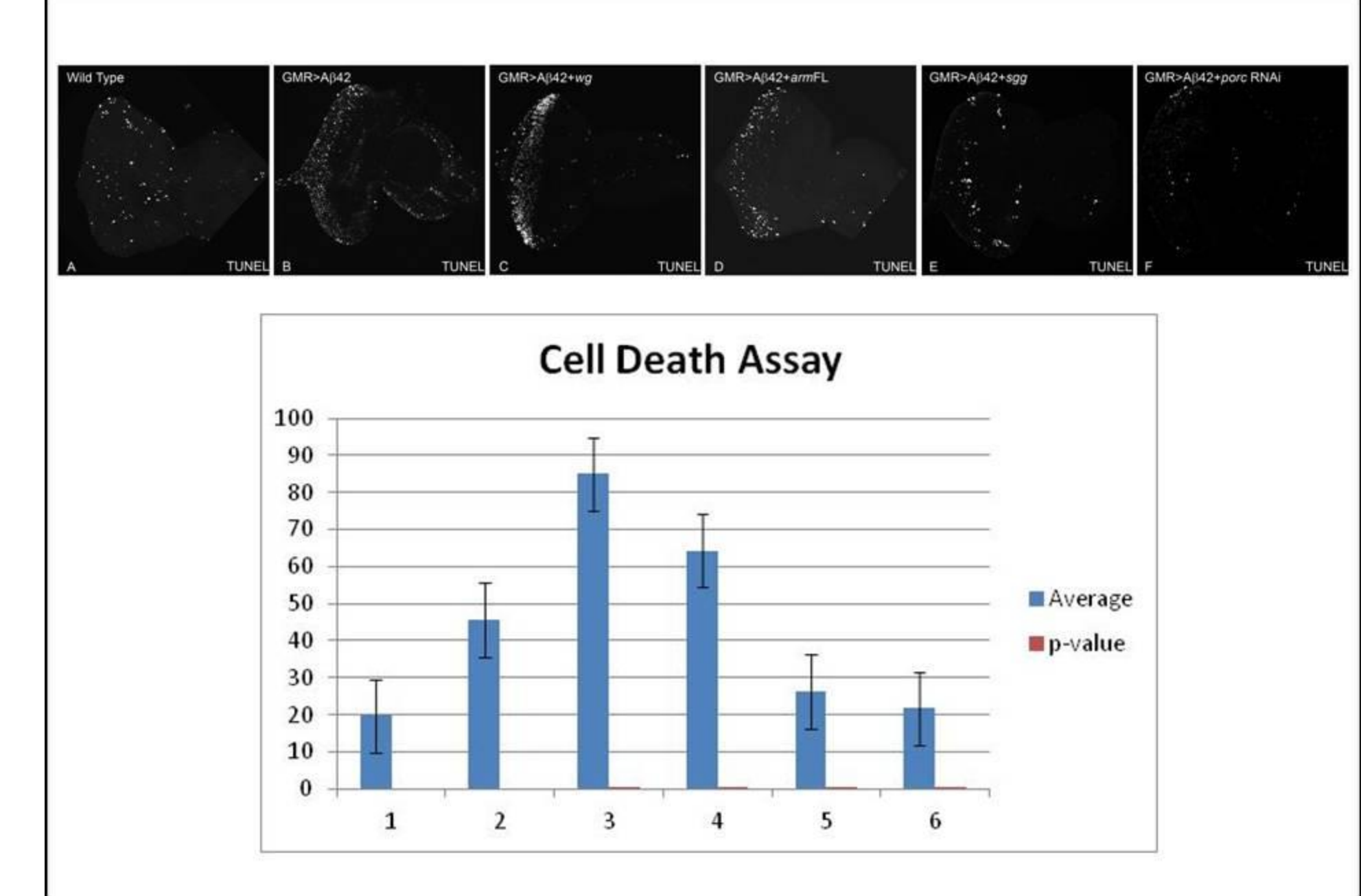
## Misexpression of A $\beta$ 42 in fly eye by GMR-GAL4 exhibits progressive neurodegenerative phenotype



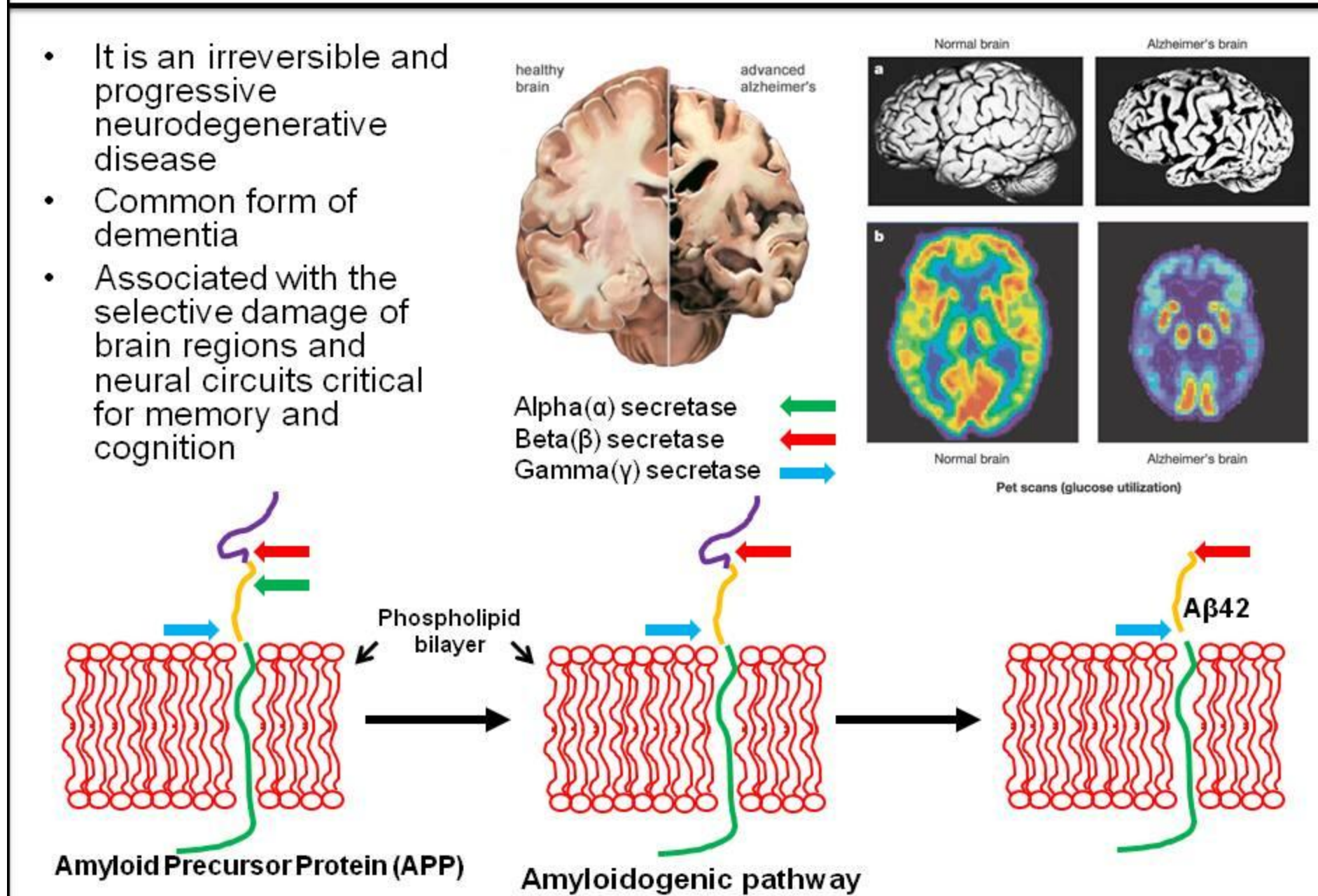
## Blocking Wg Signaling suppresses the A $\beta$ 42 mediated neurodegeneration



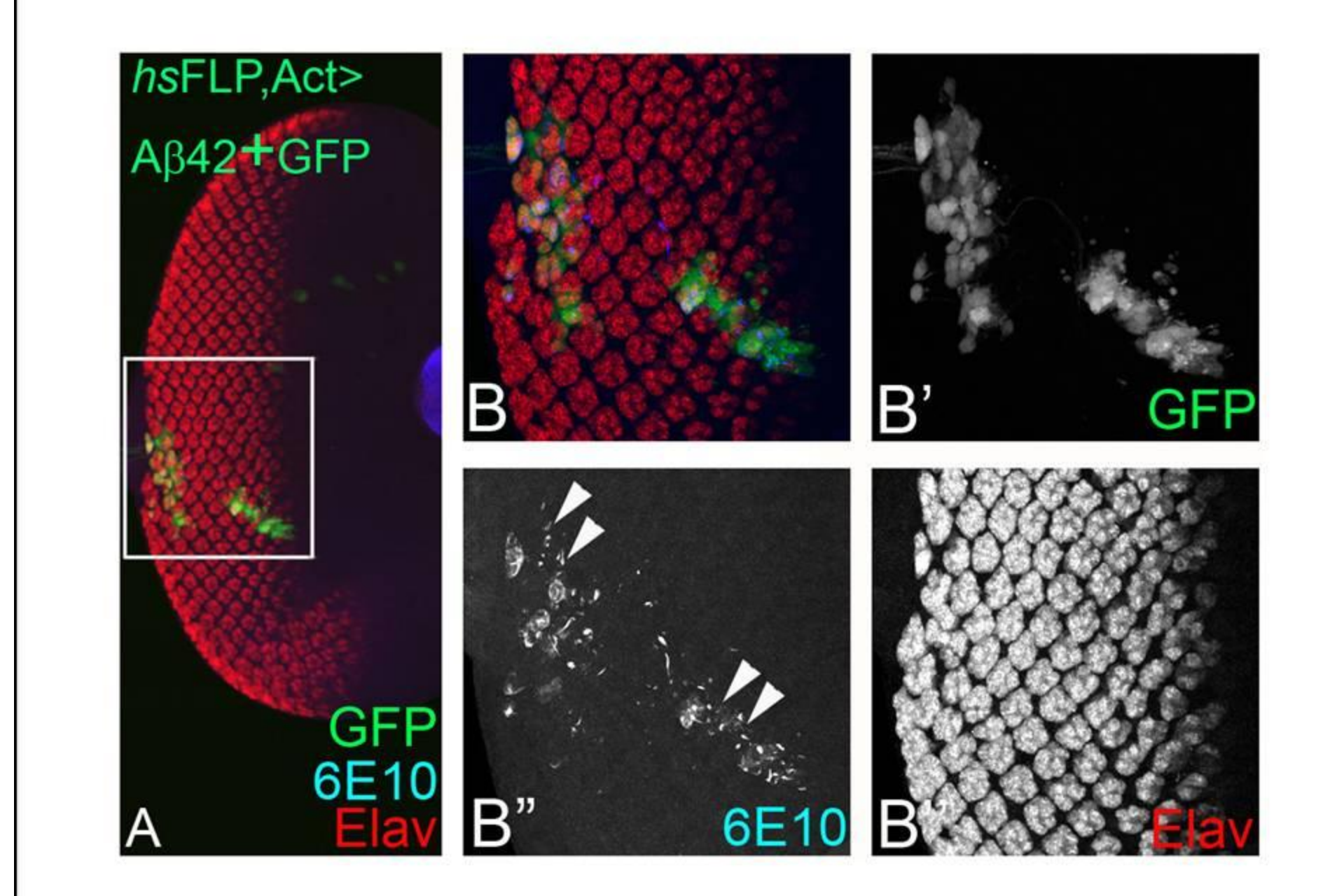
## Cell Death Assay



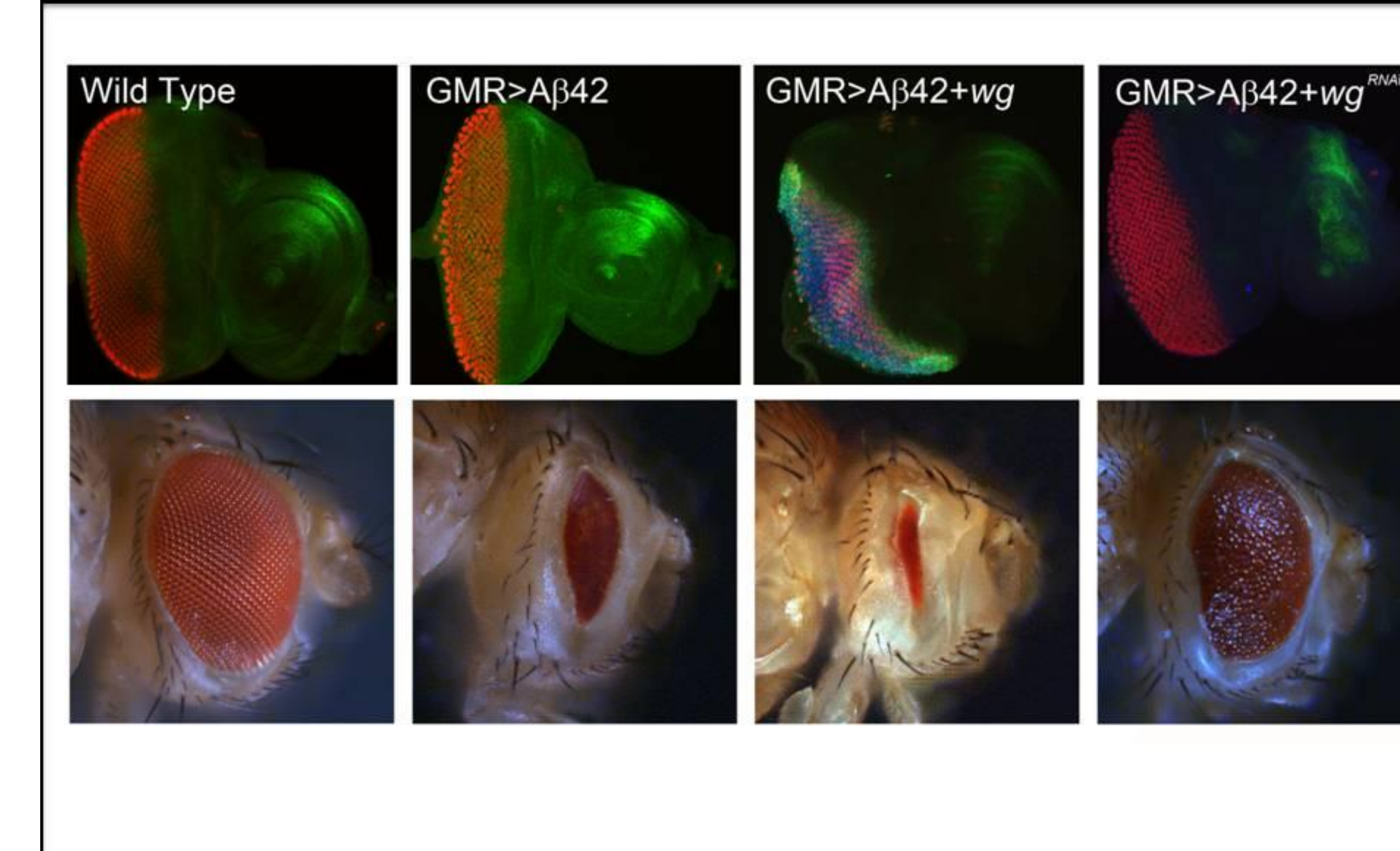
## Alzheimer's Disease



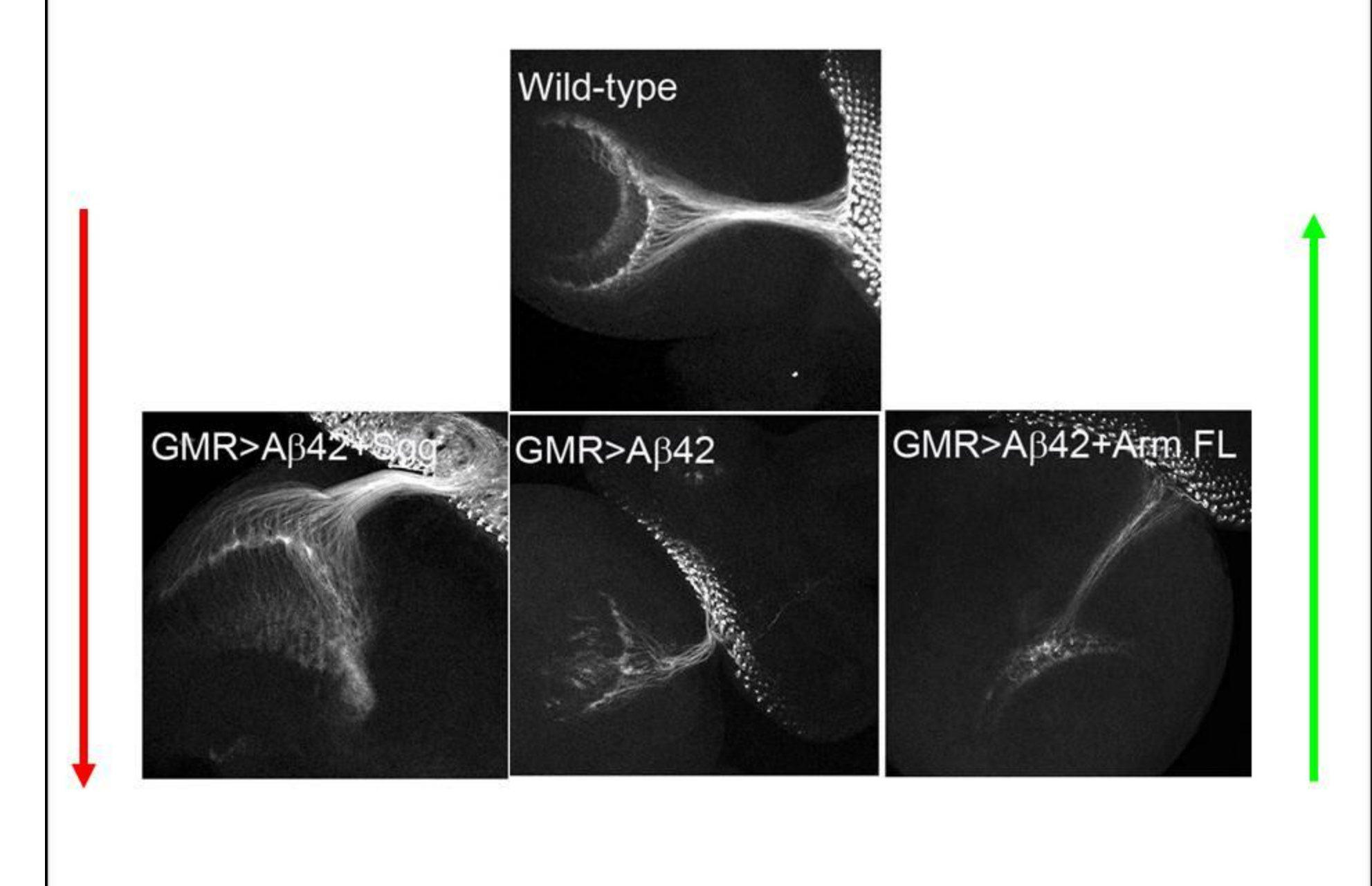
## Amyloid (A $\beta$ 42) plaques are formed in the eye



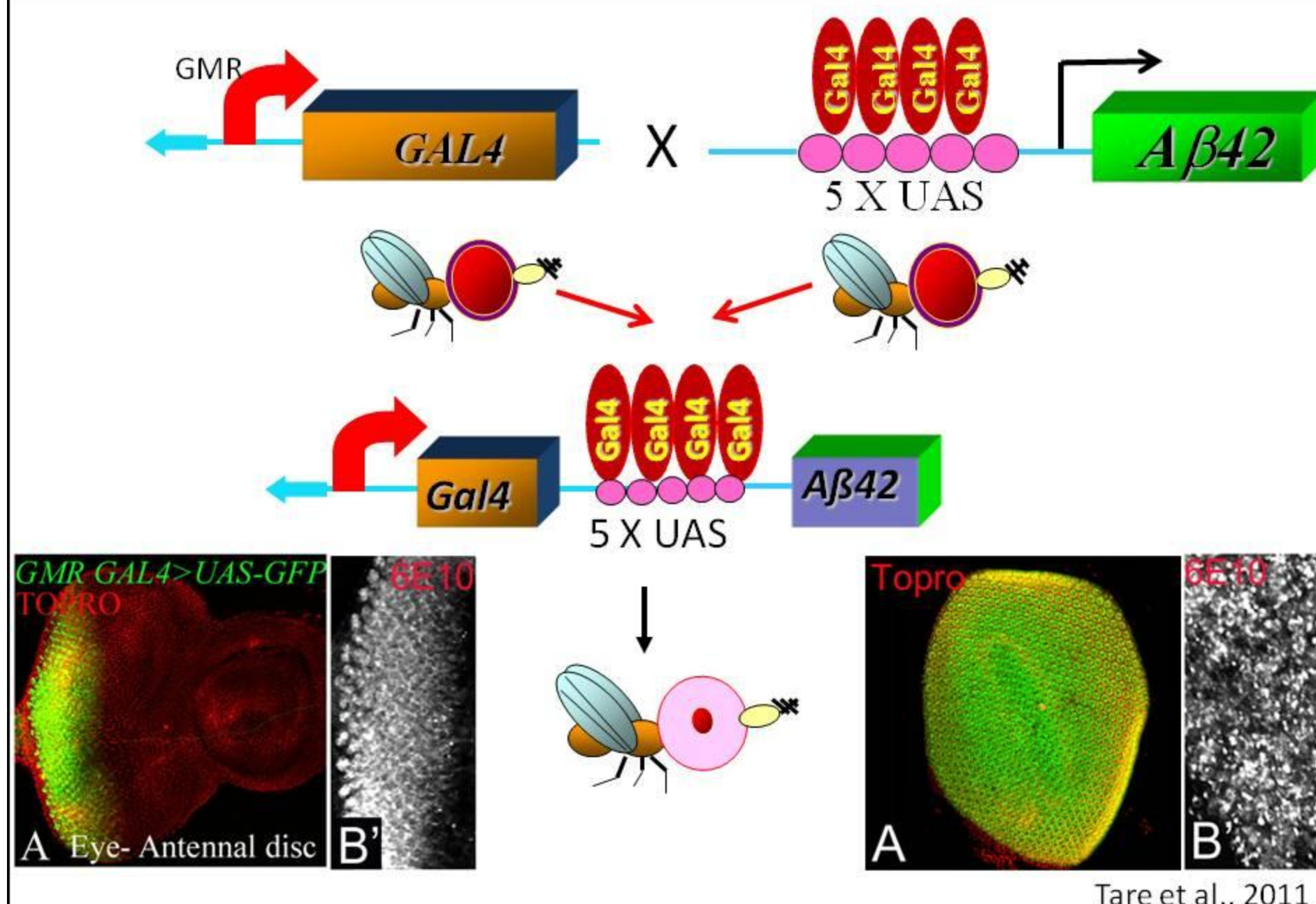
## Altering Wg levels modulates the A $\beta$ 42 mediated neurodegeneration



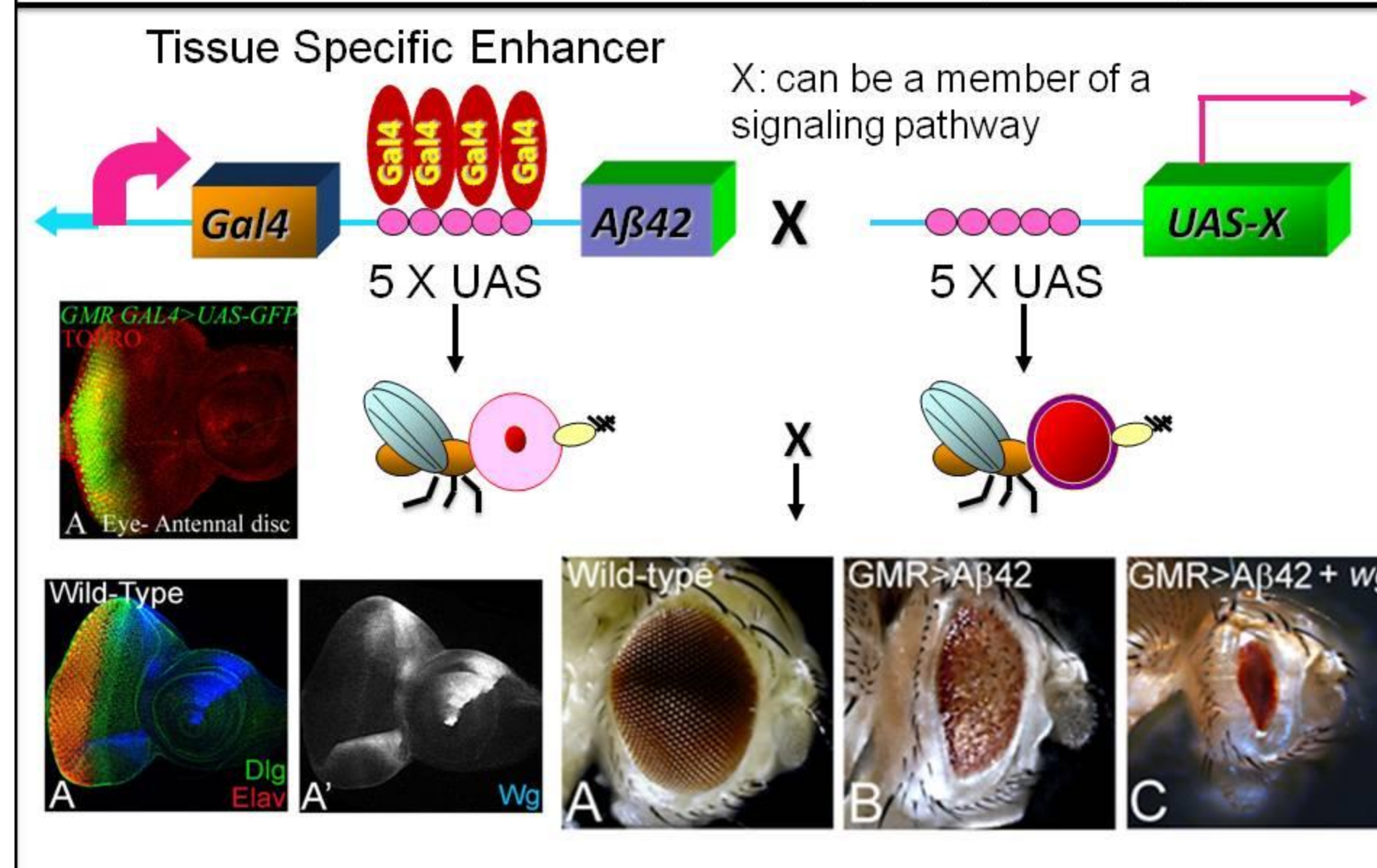
## Axonal targeting from the retina to the brain



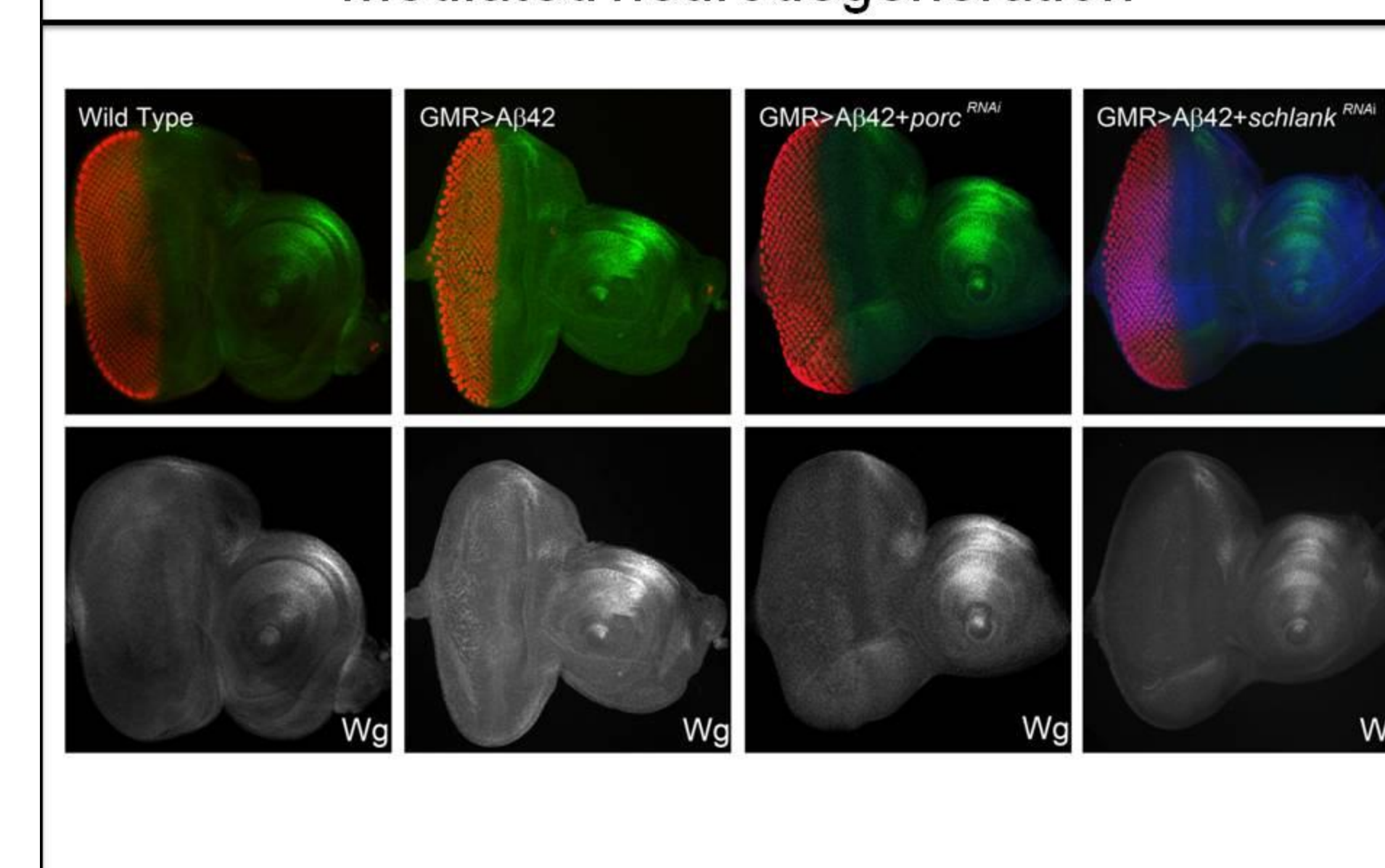
## Gain of-function approach: GAL4/UAS- System



## Strategy for the forward genetic screen to identify modifiers of GMR-Gal4>A $\beta$ 42 phenotype



## Blocking Wg transport suppresses the A $\beta$ 42 mediated neurodegeneration



## Conclusion

- 1) Activation of Wg Signaling triggers A $\beta$ 42 mediated neurodegeneration
- 2) Blocking Wg Signaling suppresses the A $\beta$ 42 mediated neurodegeneration
- 3) Wg signaling affects axonal targeting from the retina to the brain in A $\beta$ 42 background
- 4) Wg signaling triggers cell death in A $\beta$ 42 mediated neurodegeneration.
- 5) Blocking Wg transport suppresses the A $\beta$ 42 mediated neurodegeneration

